Seizure 20 (2011) 520–525

Contents lists available at ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

Antiepileptic drugs withdrawal in patients with idiopathic generalized epilepsy

Milen Pavlović [a,*], Nebojša Jović [b], Tatjana Pekmezović [c]

[a] Institute of Child and Youth Health Care of Vojvodina, Hajduk Veljkova 10, 21000 Novi Sad, Serbia
[b] Clinic of Neurology and Psychiatry for Children and Youth, School of Medicine, University of Belgrade, 6 Dr Subotica Street, 11000 Belgrade, Serbia
[c] Institute for Epidemiology, School of Medicine, University of Belgrade, Faculty of Medicine Višegradska 26, 11000, Belgrade, Serbia

ARTICLE INFO

Article history:
Received 3 November 2010
Received in revised form 4 February 2011
Accepted 18 March 2011

Keywords:
Idiopathic
Generalized
Epilepsy
Withdrawal
Antiepileptic drug

ABSTRACT

Objectives: To estimate the risk of seizure recurrence after antiepileptic drugs (AED) withdrawal and to identify related predictive features in patients with idiopathic generalized epilepsy (IGE) commencing at developing age (up to 16 year).
Methods: Medical records of consecutive patients with IGE from two refferal hospitals were evaluated between 2001 and 2009. Inclusion criteria were clinical and EEG diagnosis of IGE and follow up for at least 2 years after the AED withdrawal. The cohort consisted of 59 patients (38 females, 21 males). Follow up after withdrawal lasted 2–10 years (median 3) Time to seizure relapse and predictive factors were analyzed by survival methods.
Results: There were 21 (35.6%) patients with childhood absence epilepsy (CAE), 11 (18.6%) with juvenile absence epilepsy (JAE), 10 (16.9%) with isolated primary GTC seizures, and 17 (28.8%) with juvenile myoclonic epilepsy (JME). The relapses occured in 23 (52.2%) patients: one (6.2%) with CAE, 4 (50%) with JAE, 8 (80%) with IGE with GTC seizures and all with JME. During the first 6 months 54.5% patients relapsed (20% during withdrawal), 63.6% within 12 months, 81.8% within18 months and 95.4% within 24 months after withdrawal. Female gender, age at onset of seizures, seizure types, EEG worsening during/after AED withdrawal and age at withdrawal were significantly associated with relapse risk according to univariate analysis. In multivariate analysis, retained significant factors were: seizure types and EEG worsening.
Conclusion: Diagnosis of the specific IGE syndrome strongly affects relapse rate: the lowest was in CAE, the highest in JME. Independent risk factors for seizure relapse were: seizure type and EEG worsening during and/or after withdrawal.

1. Introduction

The impact of idiopathic generalized epilepsy (IGE) is estimated to be about 15–20% of all epilepsies.[1] The present International League against Epilepsy/ILAE/classification[2] recognizes several epileptic syndromes within IGE group. The proposed and revised classification further evolves the spectrum of IGE introducing new syndromes in development.[3]

Dynamic evolution of the known IGE syndromes and their frequent overlap often impose difficulties in determining specific IGE type in an individual patient at the disease onset as well as its prognosis.

Prognostic aspects of IGE treatment have been rarely evaluated in the literature. It is largely recognized that most of patients with IGE have good seizure control while on antiepileptic drug (AED) but uncertain prognosis after its withdrawal. In addition, there have not been randomized trials addressing in particular the optimal length of IGE treatment.

The decision about when and whether to attempt AED withdrawal during clinical remission is an old known dilemma facing both patients and clinicians. Numerous studies on AED withdrawal, have usually estimated relapse risks in heterogeneous patient cohorts regarding the type and etiology of epilepsy. Only a few studies encompassed the issues of risk of seizure recurrence after AED withdrawal in patients with different types of IGE.[4–8] So far, apart from clinical experience, no clear guidelines were given in order to answer the question of proper timing and safety of AED withdrawal in children and adolescents within particular IGE syndrome.

The main obstacle in the assessment of IGE prognosis in young patients while on treatment is the lack of reliable outcome associated predictors. Therefore, this study was aimed to estimate the relapse risk after AED withdrawal in children and adolescents up to 16 years of age, with different types of IGE and to identify factors predictive of seizure relapse.

2. Patients and methods

The study was conducted from June 2001 through December 2009. Subjects were identified among consecutive patients from

* Corresponding author. Tel.: +381 63 8652518.
E-mail address: milen_p@ptt.rs (M. Pavlović).

1059-1311/$ – see front matter © 2011 British Epilepsy Association. Published by Elsevier Ltd. All rights reserved.
doi:10.1016/j.seizure.2011.03.007

two regional referral University hospitals: Institute for Child and Adolescents Health Care in Novi Sad and Clinic for Neurology and Psychiatry for Children and Youth in Belgrade, Serbia (85 km apart from each other). Subjects as outpatients were seen by neurologists and/or neuropediatricians/epileptologists in the follow up intervals of 3–6 months, until the end of studied period.

Inclusion criteria were: diagnosis of IGE according to the ILAE criteria,[2] established clinical remission of at least two years before AED withdrawal and clinical follow up for at least two years after withdrawal or until seizure relapse. Patients were not eligible for the study if there was any doubt over the diagnosis on clinical grounds, or if all needed relevant data were not available from the case history notes. Patients who dropped out of the follow up from different reasons – non-responders or attending other Clinics were not included. For two patients, exact time of seizure relapse could not be determined.

Medical records of patients coded as IGE were evaluated during the observational period. The primary outcome end-point was seizure recurrences after the AED discontinuation. Withdrawal of AED was gradually performed in variable periods with duration ranged from 6 to 12 months.

The following variables, derived from the case records were analyzed: aside from the basic demographic ones (age and sex), age at seizure onset, type of seizure, cognitive and neurological status, history of status epilepticus, EEGs registered before, during and after AED withdrawal, records of focal EEG features, photo-paroxysmal response to intermittent photo-stimulation, AED in monotherapy vs. polytherapy, length of AED therapy, duration of the clinical remission (seizure freedom) while on AED, age at AED withdrawal, history of febrile seizures, family history for epilepsy, prenatal and/or perinatal complications and history of co-morbid pediatric disorders. These variables entered computerized database formed for all out-patients regularly examined.

3. Patient characteristics

During the investigation period, 59 patients who met all inclusion criteria were identified: females 22 (37.3%), males 37 (62.7%). The age of seizure onset was in range 4.5–16 years (median 10). At the end of the observational period the age of patients was in range 11–36 years (median 18). The duration of the follow-up since AED withdrawal in the whole group was in range 2–10 years (median 3).

Patients were classified in regard to the epilepsy syndromes. The distribution was as follows: childhood absence epilepsy (CAE) in 21 (35.6%) patients; juvenile absence epilepsy (JAE) in 11 (18.6%) patients, epilepsy with primary GTC seizures in 10 (16.9%) patients, and juvenile myoclonic epilepsy (JME) in remaining 17 (28.8%) patients.

All patients had normal neurological examination and neuroimaging (CT/MRI) findings. Cognitive status was normal in most of the patients (three patients had mild cognitive impairment). Regarding the AED therapy before withdrawal, 95.3% of patients with IGE were on monotherapy by valproic acid. The other drugs used in remaining 4.7% patients were ethosuximide and clonazepam. The AED therapy duration was in range 1–9 years (median 4). The length of stable clinical remission while on AED was in range 2.5–9 years (median 4). The age at AED withdrawal was in range 9–25 years (median 14.25).

Not any patient had the history of status epilepticus. No patients had previously suffered febrile seizure. Family history of epilepsy was noted in 11 (25%) of patients: first-grade relatives (parents and siblings) in 5 patients, second degree relatives in 5 and both degrees in one case. Pregnancy was hormonally maintained in 13% of patients. Birth was normal in all cases. Analysis of somatic co-morbidities disclosed four patients with asthma.

EEG in both settings was recorded according to the international 10–20 electrode placement system (21 channel) using Oxford Medilec EEG machine. Video-EEG become available for 5 years ago and since then it has been used as routine monitoring. Combined awake–sleep EEG was the established procedure for the AED withdrawal procedure monitoring. Awake EEG included activation procedures: hyperventilation of 3–5 min and intermittent photic stimulation. The latter was performed with stroboscopic flash at 1–30 Hz by using a light source placed 20–30 cm in front of the patients eyes. Sleep EEG was recording during spontaneous sleep or after the one night of sleep deprivation (the evening before recording) or following a partial sleep deprivation (3–4 h) the night before.

The following EEG features were registered: generalized epileptiform activity, focal epileptiform activity, abnormal activity other than epileptiform as well as photic paroxysmal reponse (PPR) if present. For the purpose of the study, records were classified, as abnormal if EEG included unequivocal epileptiform abnormalities and non-epileptiform/non-specific/abnormalities, regardless of the vigilance state during recording. If EEG recording showed the reappearance of abnormalities (spikes, spike-waves discharges, slow waves paroxysms), EEG record was marked as worsened. EEG records were performed at least once during the withdrawal period and every 3–6 months in the post withdrawal follow-up period.

4. Statistical analysis

SPSS software package for statistical analysis was used. As the main outcome measure was seizure relapse, time to seizure relapse was analyzed by Kaplan Meir method to illustrate the likelihood of seizure recurrences. Factors of possible prognostic values were evaluated by χ^2 test. Relative risks for recurrence during the follow-up were investigated by Cox regression analysis – uni/multivariate analyses[9] to allow for variable length of follow up. Outcome predictive factors were modeled according to the hazard ratio/HR/followed by the 95% confidence interval/CI. Statistical significance was accepted at $p < 0.05$.

5. Results

During the investigation period, 23 (38.9%) patients relapsed (15 had GTC type of seizure, 6 had myoclonic and 2 had combined myoclonic and absence types of seizures). In 15 (25.8%) patients EEG worsening, i.e. reappearance of epileptiform abnormalities after AED withdrawal occurred: in 5 patients with CAE, 3 with JAE and 7 with JME. That EEG aggravation was followed by the AED reintroduction. In the remaining follow up period, along with noted EEG improvement, no relapses occurred.

This group of patients, therefore, was excluded from the estimation of risk for seizure recurrence. Upon exclusion of this group of patients, seizure relapse occurred in 52.2% of the 44 patients remaining for further investigation. The Fig. 1 presents all outcome varieties after the AED withdrawal.

Regarding the recognized IGE syndrome, distribution of relapses was as follows (Table 1): CAE: only one out of 16 investigated patients with CAE (6.25%), 4 out of 8 patients with JAE (50%), 8 out of 10 patients with IGE with GTC seizures (80%) and all patients with JME (100%).

Most relapses occurred during the first year since the AED withdrawal: 54.5% patients relapsed during the first 6 months (20% of them during the AED withdrawal), 63.6% patients within 12 months, 81.8% within 18 months and 95.4% within 24 months, as shown at Fig. 2 and corresponding Table 2.

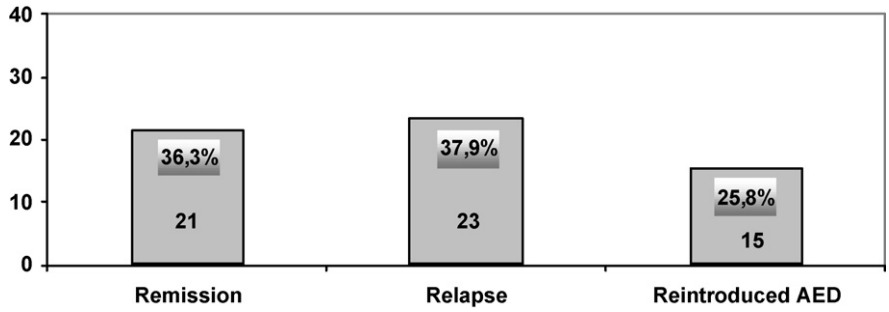

Fig. 1. All outcome varieties after the AED withdrawal.

Table 1
Seizure recurrences related to the IGE syndrome.

IGE[a] syndrome	Patients			
	Total no	Excluded due to AED reintroduction	Investigated (females/males)	Relapsed (females/males)
Childhood absence epilepsy	21	5	16 (8/8)	1 (1/0)
Juvenile absence epilepsy	11	3	8 (7/1)	4 (4/0)
Epilepsy with GTC[b] seizures	10	0	10 (8/2)	8 (7/1)
Juvenile moclonic epilepsy	17	7	10 (6/4)	10 (6/4)
Total	59	15	44 (29/15)	23 (18/5)

[a] IGE, idiopathic generalized epilepsy.
[b] GTC, generalized tonic–clonic.

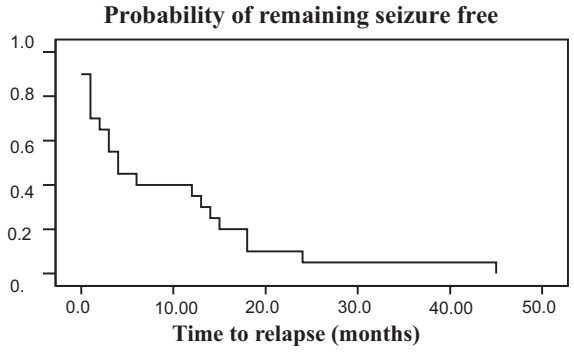

Fig. 2. Cumulative probability of stable seizure freedom following the AED withdrawal as a function of time (months) shown as Kaplan–Meier survival curve (indicating the interval between AEDs withdrawal and seizure relapse). Time 0 means the beginning of AED withdrawal.

The inter-group differences relating the occurrence of relapses for the main variables investigated are shown at Table 3. There were no significant differences between relapsed and non relapsed groups for: cognitive status, EEG record before withdrawal, focal EEG abnormalities and PPR in EEG records, duration of AED therapy, duration of seizure freedom on AED, perinatal history and family history of epilepsy. Regarding EEGs before the discontinuation of AEDs, of those who relapsed, only 3 patients had EEG abnormalities before withdrawal, including two patients with IGE with GTC seizures and one patient with JME. All patients with absence epilepsies (one patient with CAE and four patients with JAE) who relapsed had normal EEG before the AED withdrawal. The remaining 20 patients who relapsed had normal EEG records before the AED discontinuation.

Table 2
Distrubution of relapses incidence during the follow up after withdrawal.

Months	Incidence	Cummulative incidence %
0–6	12	54.5
7–12	2	63.6
13–18	5	81.8
19–24	1	95.5
25–45	1	100.0

The risk factors found to significantly affect relapse risk according to the univariate analysis were, as shown at the Table 4: female sex, age at seizure onset above 10 years, type of seizures (GTC and mixed types), abnormal EEG during/and/or after AED withdrawal and age of AED withdrawal above 15 years.

Multivariate analysis was applied in order to investigate the simultaneous influence of several factors on the relapse rate. EEG worsening during and after the AED withdrawal as well as type of seizures (GTC and combination of GTC seizures with myoclonic or absence seizures) was found to be independent risk factors in predicting the relapse risk (Table 5).

6. Discussion

Numerous studies of AED withdrawal, published so far, are mostly based on heterogeneous cohorts, consisting largely of patients with partial epilepsies.[10] There has not been a single study of that design, specifically addressed to patients with IGE having onset at developing age. Therefore, the data will be discussed in the frame of only selected relevant results from some studies.

6.1. Overall relapse rate

The rate of seizure relapses as the main outcome measure in the follow up cohorts was commonly compared among the various studies of AED withdrawal. The total relapse rate (51.2%) in this study group was higher than average ones, usually cited in AED withdrawal studies (about 30%).[12] In the study of Nicolson et al.,[6] the largest outcome study of IGE performed so far, there was also the high rate of relapses (79.9%). The study pointed that the majority of investigated patients were adults, and at least some of them might have IGE with onset in the developmental age.

6.2. Syndrome related relapse rate

Regarding particular, epileptic syndrome-related relapse rates, there were relatively small subgroups of patients available for statistical estimation. In our study, the lowest relapse rate (6.2%)

Table 3
Possible risk factors and corresponding relapse rate.

Variable	Total (*N*)	Total (%)	Relapse (*N*)	Relapse (%)	*p*
Gender					
Female	29	65.1	18	62.1	
Male	15	34.9	5	33.3	0.01
Age at epilepsy onset (years)					
<10	22	50.0	5	22.7	0.001
>10	22	50.0	18	81.8	
Type of seizure					
Absence	19	43.2	2	10.5	0.001
GTC	18	41.0	14	77.7	
Combined[b]	7	15.8	7	100.0	
Cognitive status					
Impaired	3	6.8	1	33.3	NS[a]
Normal	41	43.2	22	53.6	
EEG before withdrawal					
Normal	37	84.1	20	54.1	NS
Abnormal	7	15.9	3	42.8	
EEG during/after withdrawal					
Normal	28	63.6	12	42.8	0.011
Abnormal	16	36.4	11	68.7	
Focal EEG abnormalities					
Yes	5	12.3	4	80.0	NS
No	39	88.6	19	48.7	
PPR[c]					
Yes	16	36.4	10	62.5	NS
No	28	63.6	13	46.4	
AED therapy					
Monotherapy	42	95.5	21	50.0	NS
Polytherapy	2	4.5	2	100	
Duration of AED therapy (years)					
<4.5	26	59.1	14	53.84	NS
>4.5	18	41.9	9	50.0	
Seizure freedom on AED therapy (years)					
<4	25	56.8	14	56.0	NS
>4	19	43.2	9	44.0	
Age at withdrawal (years)					
<15	24	54.5	8	33.3	0.01
>15	20	45.5	15	75.0	
Perinatal history					
Normal	6	13.7	4	75.0	NS
Abnormal	38	86.3	19	50.0	
Family history of epilepsy					
Yes	11	25.0	6	54.5	NS
No	33	75.0	17	51.5	

[a] NS, non-significant.
[b] Combined GTC with absence and/or myoclonic seizures.
[c] PPR, photic paroxysmal response.

was found in CAE group, the highest being in JME group (100%). In a prospective study conducted by Wirrel[8] in a subgroup of 59 patients, whose epilepsy began with absence seizures, 20.3% of patients relapsed after the AED withdrawal. The relapses were considered as being result of CAE evolution to other types of IGE/7% to JME and 15% to JME. In the study of Covanis et al.,[11] 13 patients (31.5%) relapsed from 41 cases with absences who discontinued AED. At least 3 of them were considered as being evolved into JME. In our study, from 24 patients total with absence seizures (CAE plus JAE patients) only one patient of 16 belonging to CAE relapsed. In the smaller group of 8 patients with JAE, 4 patients relapsed. Taken together, the relapses ocurred in 20.8% with absence epilepsies,

Table 4
Significant predictors of seizure relapse according to univariate analysis.

Variable	HR (95% CI)[a]	*p*
Female sex	2.59 (1.21–5.21)	0.01
Age at seizure onset >10 years	4.37 (2.02–4.4)	0.001
EEG worsening during/after AED withdrawal	4.67 (1.08–12.01)	0.01
Type of seizure[b]	2.17 (1.7–2.7)	0.02
Age at AED withdrawal > 15 years	2.64 (1.4–5.0)	0.02

[a] HR, hazard risk; CI, confidence interval.
[b] GTC seizures and combined GTC seizures with myoclonic or absence seizures.

Table 5
Significant predictors of seizure relapse according to multivariate analysis.

Variable	HR (95% CI)[a]	*p*
EEG worsening (reappearance of epileptifom discharges) during and/or after withdrawal	4.00 (1.39–11.5)	0.01
Type of seizure (GTCS and combined GTCS with myoclonic or absance seizures)	2.12 (1.13–4.3)	0.02

[a] HR, hazard risk; CI, confidence interval.

which correlates approximately well with the results of mentioned studies.[8,11] In adittion, from 17 of our patients with JME there were 2 with a history of earlier absence seizures. These patients might be also regarded as cases presenting evolution from CAE to JME. Thus, these and previously reported data, favoure the view that such evolutive course is hard to predict at the time of diagnosis. In other words,remission could be predicted only by the course of epilepsy.

An interesting aspect of the issue was offered by Grosso et al.[4] who pointed that implementation of different criteria in classification of CAE (ILAE criteria vs. more strict criteria defined by Panayotopoulos) leads to different estimations concerning CAE outcome: AED withdrawal in the first case led to the relapses in 22% patients, while no one relapsed in the other case. More strict criteria were in favour of excellent prognosis for CAE. Although based on ILAE criteria, our patients with CAE had favorable outcome at the end of the follow up. However, the study of Nicolson et al.[6] of mainly adult patients reported pretty higher relapse rate for patients with CAE (65.5%).

According to the rare reports of the long-term follow up of JAE patients,[13–15] this IGE syndrome seems to have an overall lower rate of long-term remission. Our study with a small subgroup of patients pointed to the equivocal results (50% relapsed). This correlates with the results of Covanis et al.[11] where 3 out of 5 patients with JAE relapsed after AED withdrawal. Nicolson et al.[6] reported similar relapse rate of 68.4%. As far as IGE subgroup with GTC seizures is concerned, 8 out of 10 patients relapsed. No partcular attention regarding their prognosis has been observed in published literature. Maybe, the reason could be in perception that this group rather belongs to overlapping continuum of IGE syndromes. So, definitive prospect from the view of developmental period stand point is not easy to anticipate.

In our study, all studied patients with JME who discontinued AED relapsed after AED withdrawal. General impression from the published literature regards JME[15–18] as the life long epileptic condition. Canevini et al. reported relapses in all JME patients attempted to discontinue AED[19]. In some studies[6,20] the relapse rate following AED withdrawal was 93.6% and 81.8% respectfully. Considering the relapse rate for JME patients in our cohort, we were not aware what could happen to those patients who restarted AED after worsening of EEG only and without seizure relapse.

The time of relapses: most of the recurrences in our study occurred within the first two years (95.4%). More than a half of these relapses (54.5%) occurred during the first 6 months, and 18.8% during the withdrawal period. This is in concordance with previous works on overall timing of relapse in heterogeneous study groups: 85–90% of recurrences occurred within 2 years,[7,18,21] in particular during AED withdrawal and in the course of the first few months after discontinuation of therapy. That further supports the need for clinical and EEG follow up of these patients for at least during the first 2 years after AED withdrawal.

6.3. Risk factors for relapse

In comparison to factors predictive of relapses after AED withdrawal in epilepsies of non-idiopathic etiology, the investigated variables spectrum is obviously reduced (neurological status and neuroimaging findings in IGE were normal and therefore

excluded). In the investigated cohort of IGE patients, according to univariate and mutlivariate analysis, seizure type/GTC and mixed types of seizure (GTC combined with myoclonic and/or absence seizures)/and interictal EEG worsening during/after AED withdrawal were associated with significantly increased risk of seizure relapses on the follow-up.

The marked inconsistencies reported in the literature regarding the effect of seizure type on withdrawal outcome can be mostly attributed to the differences in studied population. GTC seizures during the course of disease are highlighted as significant predictor of adverse outcome in some studies,[4,13,14] which is concordant with the results of our study. In 4 out of 6 patients in our study, who had GTC seizures apart from absence seizures, relapses ocurred. These patients belonged to the JAE subgroup of patients. The long-term prognosis of this IGE syndrome was the topic of only a few studies designed not as withdrawal studies but as general outcome studies.[12–14] The results of the study conducted by Grosso et al.[4] are also in corelation to our results: the most important independent predictors of remission failure (defined as no seizures after withdrawal for more than one year) were GTC seizures and myoclonic seizures during the active disease.

Our study pointed to the importance of EEG worsening during withdrawal and after the AED withdrawal, as a solid marker for those who will relapse without medication. On the other side, inter-ictal EEG records before the AED discontinuation were not predicting for relapse. Of 23 patients who relapsed, 3 (13%) patients had EEG abnormalities before withdrawal. Reported effects of abnormal EEG prior to the AED withdrawal on relapse risk are otherwise, extremely inconsistent in the published literature.[21,22] However, results of this study indicated an association between EEG worsening (persisting and/or increased interictal epileptiform abnormalities during/after AED withdrawal) as statistically significant. This is similar with results of the study conducted by Galimberti et al.,[23] which enrolled adult patients. Andersson et al.[24] reported that persistence of generalized paroxysms of spike-waves predicted relapses during AED withdrawal. These discharges are otherwise supressed during treatment, especially in children with absence seizures before AED withdrawal. Olsson et al.[25] did not recommend AED withdrawal in patients with absence seizures as far as abnormal EEG exist. Because spike-wave paroxisms may persist during maintained clinical remission, or GTC seizures may ocurr in the absence of interictal EEG abnormalities, predictive value of EEG is relativized.[25,26] Possible influence of residual SW discharges to the outcome of epilepsy was also emphasized in the work of Camfields.[27] They warranted repeating EEG after the AED discontinuation in order to look for reappearance of epileptiform discharges. This is in accordance to our study where in 5 of our patients with CAE and in 3 patients with JAE alarming presence of interictal spike-waves prompted reintroduction of AED.

Female gender was one of the significant predictors for relapse risk according to the univariate analysis. Higher relapse rate in girls was also found in studies of Altunbasak et al. and Dooley et al.[21,28] This finding is probably reflection of female predominance over males in the study cohort especially regarding subgroups of patients with less favorable outcome/IAE, IGE with GTC seizures and JME. Relapse risk in females could also be affected by physiological hormonal disturbances related to the age at disease onset and the age of AED withdrawal. These are two further commented variables, significantly associated with relapse risk in the univariate analysis. Age at seizure onset beyond ten years of age, as the important predictor for relapse found in this study is concordant with some earlier studies.[28,29] It also correlates with poorer outcome of those IGE syndromes commencing at that age. Age of AED withdrawal, as also one of the significant variables associated with higher relapse risk, not unexpectedly, mirrored the previous finding.

Whether duration of AED treatment changes the prognosis of epilepsy or simply suppresses seizures to allow the spontaneous remission? This topic has been debated intensely. [12,22,27] Duration of AED therapy for less than 4.5 years was not significantly associated with relapse risk in the univariate analysis of our study, such not supporting the view that longer period of AED treatment enables safer discontinuation.

The study faced some limiting issues. Enrolment of sufficient number of patients was influenced by the actual representation of this type of epilepsy in the regions covered by two hospitals where investigation was conducted. Better recruitment so appeared more likely, although some patients followed by other physician at these settings might be missed. In addition, selection of patients for withdrawal of antiepileptic treatment could be biased by personal attitudes related to issues such as length of treatment and/or EEG precluding criteria.

7. Conclusion

Applying the common design of most AED withdrawal studies, this study was aimed to identify predictors of the outcome in patients with IGE when discontinuation of drugs is considered. Given the overlapping of syndromes within IGE throughout their natural history, the task was challenging.

The study results underlined the importance of syndromic attributes of specific IGE for assessing outcome after the AED withdrawal: the lowest relapse risk being in CAE and highest in JME. However, as this clear cut distinction of syndromes seems not to be always obvious at the very beginning of the disease course, knowledge of the outcome predictors could guide clinicians in a safer mode. A few prognostic factors, as independent variables emerged as valuable for the prediction of seizure recurrence in IGE: EEG worsening during and/or after the AED withdrawal and history of GTC seizures alone or in combination with other generalized seizures. Larger longitudinal studies in future, might give additional support to these data, especially in assessing the risks of withdrawal of AED in particular IGE syndromes.

Conflict of interest

None.

Acknowledgment

Tatjana Pekmezovic was supported by grant of the Ministry of Science and Technological Development of the Republic of Serbia (Grant no. 145045).

References

1. Jallon P, Latour P. Epidemiology of idiopathic generalized epilepsies. *Epilepsia* 2005;**46**(9):10–4.
2. Commission on classification and terminology of the ILAE. Proposal for revised classification of epilepsies and epileptic syndromes. *Epilepsia* 1989;**30**:389–99.
3. Commission A proposed diagnostic scheme for people with epileptic seizure and with epilepsy: report of the ILAE task Force on Classification and Terminology. *Epilepsia* 2001;**42**(6):796–803.
4. Grosso S, Galimberti D, Vezzosi P, Farnetani M, Di Bartolo RM, Bazzotti S, et al. Childhood absence epilepsy: evolution and prognostic factors. *Epilepsia* 2005;**46**(11):1796–801.
5. Kudo T, Nishida T, Yagi K. Discontinuation and duration of antiepileptic drug therapy: a retrospective study of factors for specific epileptic syndromes. *Epilepsia* 2004;**45**(Suppl. 8):26–32.
6. Nicolson A, Appleton RE, Chadwick DW. The relationship between treatment with valproate, lamotrigine and topiramate and the prognosis of the idiopathic generalized epilepsies. *J Neurol Neurosurg Psychiatry* 2004;**75**(1):75–9.
7. Schmidt D. Response to antiepileptic drugs and the rate of relapse after discontinuation in juvenile myoclonic epilepsy. In: Schmitz D, Sander T, editors. *Juvenile myoclonic epilepsy: the Janz syndrome*. Philadelphia: Wrightson, Petersfield; 2000. p. 111–20.

8. Wirrel EC. Natural history of absence epilepsy in children. *Can J Neurol Sci* 2003;**303**:184–8.
9. Cox DR. Regression models and life tables. *J R Stat Soc* 1972;**34**(Series B):187–220.
10. Shinnar S. Update on the epidemiology and prognosis of pediatric epilepsy. *J Child Neurol* 2002;**17**(Suppl. 1):S4–17.
11. Covanis A, Skiadas K, Loli N, Lada C, Theodorou V. Absence epilepsy: early prognostic signs. *Seizure* 1992;**1**:281–9.
12. Bartolomei F, Roger J, Bureau M, Genton P, Dravet C, Viallat D, et al. Prognostic factors for childhood and juvenile absence epilepsies. *Eur Neurol* 1997;**37**:169–75.
13. Tovia E, Goldberg-Stern H, Shahar E, Kramer U. Outcome of children with juvenile absence epilepsy. *J Child Neurol* 2006;**21**(9):766–8.
14. Trinka E, Baumgartner S, Unterberger I, Unterrainer J, Luef G, Haaberlandt E, et al. Long-term prognosis for childhood and juvenile absence epilepsy. *J Neurol* 2004;**251**:1235–41.
15. Wolf P. Juvenile myoclonic epilepsy. In: Roger J, Bureau M, Dravet C, et al. editors. *Epileptic syndromes in infancy, childhood, and adolescence*. London: John Libbey; 1992. p. 313–27.
16. Penry JK, Dean JC, Reila AC. Juvenile myoclonic epilepsy: long-term response to therapy. *Epilepsia* 1989;**30**(Suppl. 4):S19–23.
17. Kleveland G, Engelsen BA. Juvenile myoclonic epilepsy: clinical characteristics, treatment and prognosis in a Norwegian population of patients. *Seizure* 1998;**7**:31–8.
18. Martinez-Juarez IE, Alonso ME, Medina MT, Durón RD, Bailey JN, López-Ruiz M, et al. Juvenile myoclonic epilepsy subsyndromes: family studies and long-term follow-up. *Brain* 2006;**129**:1269–80.
19. Canevini MP, Mai R, Di Marco C, Bertin C, Minotti L, Pontrelli V. Juvenile myoclonic epilepsy of Janz: clinical observation in 60 patients. *Seizure* 1992;**1**:291–8.
20. Panayiotopoulos CP, Obeid T, Tahan AR. Juvenile myoclonic epilepsy: a 5-year prospective study. *Epilepsia* 1994;**35**(2):285–96.
21. Altunbasak S, Artar O, Burgut R, Yildiztas D. Relapse risk analysis after drug withdrawal in epileptic children with uncomplicated seizures. *Seizure* 1999;**8**(7):384–9.
22. Shinnar S, Berg AT, Moshe SL, Kang H, O'Dell C, Alemany M, et al. Discontinuing antiepileptic drugs in children with epilepsy: a prospective study. *Ann Neurol* 1994;**35**:534–45.
23. Galimberti CA, Manni R, Parietti L, Marchioni E, Tartara A. Drug withdrawal in patients with epilepsy: prognostic value of the EEG. *Seizure* 1993;**2**: 213–20.
24. Andersson T, Braathen B, Persson A, Theorell K. A comparison between one and three years of treatment in uncomplicated childhood epilepsy: a prospective study. II. The EEG as predictor of outcome after withdrawal of treatment. *Epilepsia* 1997;**38**:225–32.
25. Olsson I, Hagberg G. Epidemiology of absence epilepsy EEG findings and their predictive value. *Acta Paediatr Scand* 1991;**7**(2):100–4.
26. Koutromanidis M, Smith S. Use and abuse of EEG in the diagnosis of idiopathic generalized epilepsies. *Epilepsia* 2005;**46**(Suppl. 9):96–107.
27. Camfield C, Camfield P. Management guidelines for children with idiopathic generalized epilepsy. *Epilepsia* 2005;**46**(Suppl. 9):S112–S116.
28. Dooley J, Gordon K, Camfield P, Camfield C, Smith E. Discontinuation of anticonvulsant therapy in children free of seizures for 1 year: a prospective study. *Neurology* 1996;**46**:969–74.
29. Peters AC, Brouwer OF, Geerts AT, Arts WF, Stroink H, van Donselaar CA. Randomized prospective study of early discontinuation of antiepileptic drugs in children with epilepsy. *Neurology* 1998;**50**:724–30.